IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Tommy Ekstrom	Art Unit	: 1617
Serial No.	: 09/367,950	Examiner	: Jennifer M. Kim
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REPLY BRIEF

Pursuant to 37 C.F.R. § 41.41, Appellant responds to the Examiner's Answer, dated June 16, 2006, as follows.

Appellant's claims are generally directed to methods of prevention and treatment of asthma symptoms that include instructing a patient to inhale an effective amount of a composition that includes, in admixture, (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate of formoterol or a solvate of such a salt, and (b) a second active ingredient which is budesonide, where the patient is instructed to inhale the composition on demand (see independent claims 13, 35, 36, and 43) or as needed (see independent claim 42).

The following grounds of rejection remain:

(i) claims 13, 35, 36 and 42 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement;

(ii) claims 13-15, 17, 18, 20-36, 38, 42 and 43 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (WO 93/11773); and

(iii) claims 16 and 19 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* and further in view of Aberg *et al.* (U.S. Patent No. 5,795,564) and Ryrfeldt *et al.* (*Biochem. Pharmacol.* 38:17-22, 1989, Abstract).

Each of these grounds for rejection is addressed in turn below.

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(i) Rejection of claims 13, 35, 36 and 42 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement

The Examiner has found the rejected claims to be enabled as far as they are directed to methods of treatment, but maintains that the claims are not enabled as far as they are directed to methods of prevention. The Examiner states in the Examiner's Answer, as she did in the Final Office Action (dated September 21, 2005), that "the specification, while being enabling for the 'treatment of an acute episode of asthma,' does not reasonably provide enablement for the 'prevention of an acute episode of asthma'." Examiner's Answer at page 3.

For the sake of accuracy, Appellant first wishes to point out that none of the claims uses the language put in quotes by the Examiner ("treatment of an acute episode of asthma" and "prevention of an acute episode of asthma"). Claim 43 comes the closest in that it is drawn to "A method of reducing the incidence of acute asthma attacks," but it does not mention the word "prevention" *per se* and indeed is not rejected for lack of enablement.[1] All of the other pending claims are drawn to methods of "prevention and treatment of asthma symptoms," and not "prevention and treatment of an acute episode of asthma" as assumed by the Examiner.

As Appellant noted at page 4 of the Appeal Brief submitted March 3, 2006 (hereafter the "Appeal Brief"), the standard for enablement is whether any experimentation needed to practice the invention is undue. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). In Wands, the Federal Circuit set forth the criteria for determining whether the amount of experimentation is undue. These criteria include: (i) quantity of experimentation necessary, (ii) amount of direction or guidance presented, (iii) presence or absence of working examples, (iv) nature of the invention, (v) state of the prior art, (vi) relevant skill of those in the art, (vii) predictability or unpredictability of the art, and (viii) breadth of the claims. Id. Appellant addressed many of these factors in the Appeal Brief, and the Examiner commented specifically on a few of these at pages 10-11 of the Examiner's Answer. Rather than repeat what was already said in the Appeal Brief, Appellant's comments below are limited to addressing these specific remarks by the Examiner.

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[1] Appellant notes for the record the obvious: a method of "reducing the incidence of acute asthma attacks" of course broadly encompasses methods of preventing at least some of those attacks.

Relevant skill of those in the art. The Examiner states that "the relative skill of those in the art is quite high and weighs in favor for the **aspects** of 'treatment' of asthma, however, the remaining factors of 'prevention' weigh against because there is **no absolute 'prevention'** of such disease." Examiner's Answer at pages 10-11 (emphasis in original). It is not clear just what the Examiner was trying to communicate here. If she means that the relative skill in the art of "preventing" asthma is low because it is impossible to prevent asthma, Appellant must disagree. First, whether it is possible to prevent asthma is not the issue, since the claims are not drawn to methods of "preventing asthma." The claims that mention prevention *per se* are drawn to methods of prevention or treatment of asthma symptoms, not asthma *per se*. Second, preventing the symptoms of asthma is routinely done by the same highly-skilled physicians who treat asthma symptoms—indeed, the nature of the disease means that the two concepts overlap to some extent. Such physicians know to instruct their patients to use the appropriate drugs whenever they believe that asthma symptoms are imminent: *e.g.*, when they are about to exercise (for patients who have exercise-induced asthma) or to enter pollen season (for patients who have pollen allergies that trigger asthma attacks), in order to prevent asthma symptoms in those patients. They also know how to prescribe drugs that keep airway inflammation under control, thereby reducing the likelihood of (*i.e.*, "preventing") the development of asthma symptoms. It is therefore difficult to see how these physicians could be characterized as being anything but of "high" skill in the art of something they strive to do with all of their asthma patients every day: preventing asthma symptoms.

The above is so self-evident that Appellant believes the true issue here stems from the Examiner's misconception that the term "prevention" implies some absolute that can never be reached: that the claimed method must be 100% effective, 100% of the time, in 100% of patients. That sort of absolute standard has never been the standard under U.S. law for enablement of methods of treatment, and Appellant does not see why the Examiner is assuming it is the standard (if indeed she is) for the presently claimed method of prevention. Selecting a very narrow interpretation that is at one far extreme of the scope of the claim is directly contrary to the directive that during patent examination, the claims must be "given their broadest

reasonable interpretation consistent with the specification. In re Hyatt, 211 F.3d 1367, 1372 (Fed. Cir. 2000). See also MPEP 2111. For any invention in any field, it is always possible to imagine some embodiment that would not be expected to work. For the Examiner to arbitrarily select one such embodiment, limit the claims to it, and then declare the claims not enabled, is not appropriate. The Examiner is reminded of her burden under the enablement requirement as described in MPEP 2164.04, citing Genentech v. Wellcome Foundation, 29 F.3d 1555, 1563-64, 31 USPQ2d 1161, 1167-68 (Fed. Cir. 1994):

> Before any analysis of enablement can occur, it is necessary for the examiner to construe the claims. For terms that are not well-known in the art, or for terms that could have more than one meaning, it is necessary that the examiner select the definition that he/she intends to use when examining the application, based on his/her understanding of what applicant intends it to mean, and explicitly set forth the meaning of the term and the scope of the claim when writing an Office action. (Emphasis added).

A person having ordinary skill in the art would understand that Appellant intended the term "prevention of asthma symptoms" to have its ordinary meaning, *i.e.*, that asthma symptoms are reduced in frequency and/or severity. A reduction in frequency means that some episodes that would otherwise have occurred, do not occur (*i.e.*, are *prevented*). A reduction in severity means that the most severe symptoms, such as great discomfort and/or inability to breathe, do not occur (*i.e.*, are *prevented*). Such an interpretation is broad enough to encompass complete avoidance of all asthma symptoms in a given person, but certainly is not limited to that extreme. Appellant requests that the Board substitute an interpretation of "prevention" in line with what Appellant intended it to mean, and what one of ordinary skill in the art would consider reasonable.

Amount of direction or guidance presented. The Examiner states that the "amount of direction of [sic] guidance provided can only be described as minimal." Examiner's Answer at page 11. She further states that "[t]here is no evidence of record that asthma can be **absolutely prevented** by any compound." Id. (emphasis in original). As discussed above, Appellant strongly disagrees with the Examiner's all-or-nothing view regarding the definition of "prevention". The word "absolutely" does not appear in the claims and has been inappropriately

read into the claims by the Examiner. The extreme and narrow definition arbitrarily selected by the Examiner is not consistent with the way the term is used in the specification nor the way it is used in the art, as evidenced by multiple publications cited by Appellant in the Appeal Brief. If the term "prevention" is given a more normal interpretation than that selected by the Examiner, one can readily see that it is enabled by the guidance provided in the specification.

That the specification discusses the details of how to accomplish both treatment and prevention of asthma symptoms was elaborated in the Appeal Brief on pages 6-7 and is mentioned again here only because the Examiner does not seem to recognize that fact, instead continuing to characterize the amount of guidance in the specification as "minimal." For example, the specification at page 3, lines 7-19, states:

> Acute asthma attacks may occur on an irregular basis when exposed to an agent e.g. during the pollen season, a virus infection, cold air, perfumes or any other agent(s) triggering an asthma attack in the patient.
>
> It lies within the scope of the present invention to use the compositions comprising active compounds (a) [a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt] and (b) [a second active ingredient which is budesonide] for <u>treating</u> acute conditions of asthma, intermittent asthma and episodes of chronic asthma, in addition to treating chronic asthma on a regular basis, with the same active compounds...
>
> We contemplate <u>preventive</u> use when the patient expects to encounter asthma inducing conditions e.g. intends to take exercise or go into smoky conditions. (Emphasis added).

As noted at pages 6 and 7 of the Appeal Brief, further guidance regarding appropriate formulations, dosage, delivery, *etc.* are also provided in the specification. For example, the specification at page 1, lines 11-15, indicates that the teachings in the specification apply to both prevention and treatment:

> The invention further relates to a method for <u>prevention or treatment</u> of an acute condition of asthma and/or intermittent asthma and/or episodes in chronic asthma by administering, by inhalation, a composition comprising the first and second active ingredients as defined previously. (Emphasis added).

This description of the method as including both prevention and treatment is reiterated in the specification at page 3, lines 21-27, where the composition is more explicitly described as containing (a) formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and (b) budesonide. The specification also provides on pages 5-9 detailed teachings regarding formulations, ratios of the active ingredients, doses, types of inhalers, *etc.*, **all of which apply equally to use for prevention or treatment**.

The Examiner points to examples 5 and 6, alleging that "[a]ccording to the specification the subject being administered with the combinations are for the **treatment** of **sporadic breakthrough symptoms** (Example 5) and **having the symptoms of asthma** (Example 6)." (Emphasis in original). This is not a fully accurate characterization of these prophetic Examples. Example 5 teaches that a patient on "maintenance treatment" with the fixed combination "additionally uses the same combination either for rescue purposes once or twice daily to treat sporadic breakthrough symptoms, or as needed to treat exacerbations during one or two weeks." As indicated by the O'Byrne *et al.* publication ("Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever medication in Asthma," *Am. J. Respir. Crit. Care Med.* 171:129-136 (2005); Exhibit D in the Evidence Appendix filed with the Appeal Brief), that regimen of maintenance treatment plus further doses as determined by the patient to treat symptoms or exacerbations is very effective in *preventing* many exacerbations that would otherwise have occurred. See, *e.g.*, the first bar graph of Figure 1B on page 132 of O'Byrne *et al.*, which concerns *prevention* of severe exacerbations, and also Table 2 on page 133, which concerns prevention of both mild and severe exacerbations. *Prevention* of exacerbations, of course, means that at least some asthma symptoms (the most severe, life-threatening ones, in fact) are also *prevented*. Thus, Example 5 of the specification clearly provides guidance in how to *prevent* at least some asthma symptoms.

Likewise, Example 6 of the specification is relevant to the "prevention" aspect of the invention:

> A patient with intermittent asthma uses the fixed combination formoterol fumarate dihydrate/budesonide as sole medication to be taken as needed until the asthma

> resolves....**If symptoms still persist** after that period of time [8-120 weeks]—regular maintenance therapy should be considered.

By describing an alteration in the treatment plan "[i]f symptoms still persist" after the patient takes the combination on an "as needed" basis for a period of time, the Example implies that "as needed" administration (*i.e*, when the patient senses the first symptoms that precede an exacerbation) is expected to largely *prevent* development of other asthma symptoms—*i.e.*, the symptoms associated with a full-blown exacerbation. In addition, the budesonide part of the combination is expected to produce relatively long-lasting anti-inflammatory effects, thereby *preventing* future episodes of bronchoconstriction in much the same way that maintenance treatment would do. This is explained in the specification at page 4, lines 7-23. In other words, Example 6 describes a prophetic use of a method of the invention whereby one can *prevent* at least some asthma symptoms in a patient with intermittent asthma.

Even without these two prophetic examples, however, Appellant's specification amply teaches how to carry out the claimed methods of prevention and treatment, and the O'Byrne *et al.* publication shows that Appellant's assertions regarding both prevention and treatment are correct.

The discussion of the enablement rejection in the Examiner's Answer concludes on page 11 by making it clear that the rejection hinges on the Examiner's interpretation of "prevention" as being limited to what she terms "absolute prevention":

> There is no evidence of record that asthma can be **absolutely prevented** by any compound. The quantity of experimentation required to practice the absolute prevention would be considerable. For this reason, analysis under the Wands factors conclude [sic] that appellant's disclosure would not enable a person of skill in the art to practice the claimed invention of **absolute "prevention" without undue experimentation.** (Emphasis in the original)

This serves to illustrate that the Examiner is completely out of touch with how the specification and the art use the term "prevention" in the context of asthma symptoms. Although Appellant has pointed this out repeatedly during prosecution, the Examiner persists in applying her own extraordinarily narrow and extreme interpretation, rather than the one that is intended by

Appellant and that is reasonable in view of how the art uses the term. There is simply no question that Appellant has enabled one of ordinary skill to practice the claimed methods of prevention and treatment, as properly interpreted.

Other Wands factors were discussed at length in the Appeal Brief (see pages 5-12), and the Examiner has not commented on these points. Appellant therefore directs the Board to the Appeal Brief for further discussion related to the enablement issue.

Appellant maintains that in view of the arguments presented above, in the Appeal Brief and throughout the prosecution history, the claims are fully enabled with respect to both the treatment and prevention aspects. Appellant therefore respectfully requests that the Board reverse the rejection under 35 U.S.C. § 112, first paragraph.

(ii) Rejection of claims 13-15, 17, 18, 20-36, 38, 42 and 43 for obviousness over Carling *et al.*

Claims 13-15, 17, 18, 20-36, 38, 42 and 43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Carling *et al.* (WO 93/11773, "New Combination of Formoterol and Budesonide").

The Examiner reiterates the justification for the rejection at page 8 of the Examiner's Answer by stating:

> The difference between Carling *et al.* and Applicant's invention is instructing a patient to inhale, on demand, as determined by the patient based on the patient's symptoms...
>
> However, to instruct the patient to inhale, on demand, as determined by the patient's symptoms in acute asthmatic episode is obvious since Carling *et al.* teach that the dosages strongly depend on the severity of disease...and the suitable daily dosage is up to 8 inhalation.

Appellant has rebutted this viewpoint throughout the prosecution of this case, as well as in the Appeal Brief, by pointing out, *inter alia*, that Carling *et al.* at page 4, lines 19-21, states that "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." (Emphasis added). Similarly, Carling

at page 6, lines 22-29, says, "The intended dose regimen is a twice daily administration..." Appellant also submitted arguments and extrinsic evidence to show that at the publication date of Carling *et al.* (June 24, 2003), a person having ordinary skill in the art of asthma therapy would not have been motivated to instruct a patient to inhale a composition comprising both budesonide and formoterol more than twice daily, or to instruct a patient to inhale the composition on demand, or as needed, such that the therapy would be administered more than twice daily. This extrinsic evidence is discussed in greater detail below.

Appellant has also objected throughout the prosecution of this case to the Examiner's insistence that Carling can be read to contemplate up to 8 inhalations per day. The Examiner maintains at pages 11-12 of the Examiner's Answer that

> while Carling et al. teach the twice a day dosing administration, Carling et al. also teach that the regimen also depend on the severity of the disease as well as patient's physiology [Carling et al. at page 6]...Carling et al. also provide working examples comprising amounts of active agents per doses of inhalation, which one of ordinary skill in the art could easily calculate up to 8 inhalations per day without going over the maximum daily dosage taught by Carling et al. on page 6, lines 21-29.

Appellant reiterates that Carling *et al.* does not teach more than a twice daily administration of a composition containing formoterol and budesonide. The Examiner seems to have arrived at this calculation of up to 8 inhalations per day by comparing the amount of active ingredient in the formulations described at pages 7-9 of Carling to the maximum dosage per day recited at page 6, lines 21-29 of Carling. For example, the Examiner may be interpreting these passages of Carling as suggesting that one might inhale eight "puffs" from an inhaler that delivers a combination of 12 μg formoterol and 100 or 200 μg budesonide per puff without exceeding what Carling *et al.* teaches is the upper end of the range of a suitable daily dose of formoterol (100 μg) and the upper end of the range of a suitable daily dose of budesonide (4800 μg). In doing so, the Examiner is ignoring the statement in Carling that "The intended dose regimen is a twice daily administration" (Carling at page 6, lines 21-22 (emphasis added)), and has also failed to consider the state of the art at the publication date of Carling *et al.*

As noted above and also at page 16 of the Appeal Brief, the Examiner recognizes that Carling does not teach that the patient should be instructed to inhale the composition on an "on demand" or "as needed" basis ("The difference between Carling *et al.* and Applicant's invention is instructing a patient to inhale on demand, as determined by the patient based on the patient's symptoms..." See, *e.g.*, Examiner's Answer at page 8.). However, the Examiner concludes that

> [it] would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the regimen according to patient's severity of condition up to maximum safe dose in order to effectively treat sporadic asthmatic symptoms when the patient experiences it in order to avoid life threatening asthmatic episodes. Examiner's Answer at page 12.

As was explained in the Appeal Brief and is reiterated below, one of skill in the art at the priority filing date of the application (June 11, 1998) would not have read Carling *et al.* to mean that the patient himself could modify the dosage of the composition "on demand" or on an "as needed basis." Instead, it would have been understood that only a physician would modify a patient's dosage.

Appellant presented exhibits with the Amendment dated June 29, 2005, and again with the Appeal Brief to show that from a date prior to the present priority date to as late as 2003, glucocorticosteroid-containing therapeutics were routinely prescribed for fixed-dosage use twice per day as maintenance therapy, with the patient forbidden to vary daily dosage outside that regimen, whether "on demand," "as needed," or for any other reason. That evidence, discussed again in some detail below because the Examiner's Answer simply dismisses it as "not persuasive," indicates that a person of ordinary skill in the art would not interpret Carling *et al.* as suggesting that a patient could vary his own dosage on demand according to the severity of his disease.

Among the exhibits presented with the Appeal Brief is a product insert packaged with the Pulmicort® Turbuhaler® (a composition containing budesonide alone) for maintenance treatment of asthma (see Exhibit A). This product insert repeatedly and emphatically instructs the patient not to take more or less than the exact dose prescribed by the physician, regardless of whether

the patient is feeling better or worse on any given day. Furthermore, the doses listed in a table at page 4, section A of exhibit A are to be administered twice daily.

Exhibits B and C submitted with the Appeal Brief are product inserts for two different combination glucocorticosteroid/ bronchodilator inhalation products. (The budesonide of the present claims is a glucocorticosteroid, and the formoterol of the present claims is a beta-2 agonist bronchodilator.) Exhibit B is a product insert (circa 2001) for the SYMBICORT® TURBUHALER®, a budesonide/formoterol inhalation powder product similar to that disclosed by Carling *et al.* The recommended dosage is 1-2 inhalations twice daily (Exhibit B, page 1, section A), and when control of symptoms is achieved with the twice daily regimen, the physician can choose to reduce the number of inhalations to one daily (Exhibit B, page 1, section B). **There is no suggestion anywhere in the document that the patient can be instructed to take the composition "as needed."** The insert in fact instructs quite the opposite: "If patients find the treatment ineffective, **or exceed the current dose of the fixed combination, medical attention must be sought**." Exhibit B at page 2, section D (emphasis added).

Exhibit C is the Patient's Instructions for Use (March 2003) for the combination product Advair Diskus® fluticasone propionate/salmeterol xinafoate inhalation powder product. (Fluticasone propionate is a glucocorticosteroid, and salmeterol xinafoate is a beta-2 agonist.) This combination product is prescribed for use twice per day, at a dose set by the physician. The product insert emphasizes repeatedly that the product must be used neither more nor less often than instructed by the physician. The patient is adamantly instructed not to use the combination therapy more frequently than 2 times daily, spaced approximately 12 hours apart, and is told to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms. Thus, even as late as 2003, glucocorticosteroid-containing inhaled therapeutics were routinely prescribed solely for fixed-dosage use as maintenance therapy, and not for immediate relief of worsening symptoms. As emphasized in the Appeal Brief, one of ordinary skill in the art of inhaled glucocorticosteroid therapy for treatment of asthma would have understood in 1998 that patients were never instructed to take inhaled glucocorticosteroids on an "as needed basis." Carling *et al.* would not have been read to suggest otherwise.

Exhibit D is the O'Byrne *et al.* reference discussed above with respect to the enablement rejection, and Exhibit E is an editorial (Barnes, "A Single Inhaler for Asthma?" *Am. J. Respir. Crit. Care Med.* 171:95-96, 2005) that comments on the clinical study presented in O'Byrne *et al.* As discussed at page 23 of the Appeal Brief, Dr. Barnes states his opinion that "**the study by O'Byrne and his colleagues may lead to changes in the paradigm of asthma management...**" Exhibit E at page 95, last paragraph. Dr. Barnes also states:

> The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. Barnes at page 95, col. 1, last paragraph.

Dr. Barnes further explains why permitting patients to take the combination drug on an "as-needed" basis was not previously contemplated: **"A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid."** Id. at page 95, col. 1-2. He then notes that this turned out not to be a problem in practice. The patients instructed to take the budesonide/formoterol combination on an as-needed basis inhaled on average only one additional dose per day, yet this approach was more effective in preventing exacerbations than doubling the fixed daily amount of budesonide had proven in a different study. Dr. Barnes calls these results "surprisingly good." Id. at page 95, col. 2, first full paragraph. As pointed out in the Appeal Brief at page 24, the comments by Dr. Barnes, including the characterization of the O'Byrne *et al.* report as including "surprisingly good results," were made in 2005, twelve years after Carling *et al.* was published. Objective indicia, such as skepticism of experts, are relevant to the issue of obviousness and must be considered in every case in which they are present. MPEP 2141 (II). Initial incredulity and skepticism by experts and others in the field, followed by surprise and ultimately acceptance, are evidence that an invention is not obvious in light of the prior art. Burlington Industries, Inc. v. Quigg, 822 F.2d 1581, 3 USPQ2d 1436 (Fed. Cir. 1987). Barnes' objective characterization of Appellant's treatment as "remarkable" and the

results as "surprisingly good" certainly qualifies as strong evidence of nonobviousness. It is difficult to see why an expert in the field would have used those laudatory terms if the treatment method had been known in the art ever since Carling was published 12 years previously.

The Board is directed to pages 17-23 of the Appeal Brief for a more detailed discussion of the exhibits. This extrinsic evidence provides insight into the state of the art of asthma research at the filing date of the application, and indicates that it would not have been obvious to a person having ordinary skill in the art to instruct a patient to modify the dosage on an as-needed basis, or to administer the combination therapy (or any budesonide-containing medicament) more than twice per day.

The Examiner states:

> It is routine practice for the one of ordinary skill in the art to adjust, and instruct the patient to prepare for the daily maintenance and emergency situation wherein the severity asthmatic attacks. In this case, it is clear that one of ordinary skill in the art would instruct the patient to take additional dosage within the maximum dosages taught by Carling et al. for the specific combination therapy to cover the emergency asthmatic attacks in order to avoid life threatening situation because the daily maximum dosage is taught and the adjustment of the dosage by the severity of the disease state is also taught. Examiner's Answer at page 13.

However routine it may have been for asthma patients to take short term bronchodilators on an as-needed basis, when an attack was imminent, it was never "routine practice" to take budesonide or other glucocorticosteroids "as needed." In view of the evidence Appellant presented to establish the state of knowledge in the field of asthma therapy at the filing date of the application, and at the publication date of Carling *et al.*, it is clear that the Examiner is using impermissible hindsight to evaluate the claims. As explained at page 24 of the Appeal Brief, to reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the Appellant's invention was unknown and just before it was made. "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718 (Fed. Cir. 1991). In

view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. MPEP 2141. The exhibits presented with the Appeal Brief, and with the Response to Office Action submitted June 29, 2005, help to establish the level of ordinary skill in the art at the filing date of Appellant's application. That art "knew" that glucocorticosteroids are potent drugs that can produce dangerous side effects if administered at dosage levels higher than warranted for the given patient. One of ordinary skill in the art at this time would not have interpreted Carling *et al.* as teaching that the combination therapy could be administered more than twice daily, and certainly not that one can leave it to the patient to determine for his or herself how many doses to take on an as-needed basis.

Appellant described in the Appeal Brief the Examiner's failure to meet her burden of establishing a *prima facie* case of obviousness (see the Appeal Brief at pages 24-27), and further presented evidence of nonobviousness through a discussion of several Graham-derived categories (see the Appeal Brief at pages 27-31). Appellant will not repeat that discussion here, instead directing the Board's attention to the Appeal Brief.

In view of the arguments presented above, in the Appeal Brief, and throughout the prosecution history, Appellant maintains that claims 13-15, 17, 18, 20-36, 38, 42 and 43 are not unpatentable over Carling *et al.*, and respectfully requests that the Board reverse the rejection under 35 U.S.C. § 103(a).

(iii) Rejection of claims 16 and 19 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* and further in view of Aberg *et al.* (U.S. Patent No. 5,795,564) and Ryrfeldt *et al.* (*Biochem. Pharmacol.* 38:17-22, 1989, Abstract).

The Examiner did not respond to Appellant's comments in the Appeal Brief regarding this grounds of rejection. Appellant therefore maintains that in view of the arguments presented in the Appeal Brief and throughout prosecution, claims 16 and 19 are not unpatentably obvious over the prior art, and Appellant respectfully requests that the Board reverse the rejection of these claims under 35 U.S.C. § 103(a).

For these reasons, and the reasons stated in the Appeal Brief, Appellant submits that the final rejection should be reversed.

No fees are believed to be due. If this is incorrect, any necessary charges, or any credits, should be applied to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188001.

Respectfully submitted,

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